REMARKS

A. Request for Reconsideration

Applicants have carefully considered the matters raised by the Examiner in the outstanding Office Action but remain of the opinion that patentable subject matter is present. Applicants respectfully request reconsideration of the Examiner's position based on the above amendments to the claims, the attached Declaration, the two Terminal Disclaimers and the following remarks.

B. Claim Status and Amendments

Claims 21-46 are pending in this application. Claim 21 has been amended herein to more particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Respectfully, no new matter has been added by way of this amendment.

C. Claim Rejection Under 35 U.S.C. §112 Second Paragraph

The Examiner has rejected Claims 21-45 as being unclear as to what constitutes "substantially no chlorinated solvent".

Claim 21 has been amended herein to recite that the liposome has no chlorinated solvents in an amount of not more

than 10 μg per liter. Support for this amendment can be found, for example, on page 27 at line 15. In light of the present amendment, Applicants respectfully request reconsideration and removal of this rejection.

D. Prior Art Rejection

The Examiner had made the following two rejections:

(1) Claims 21-43 had been rejected as being unpatentable over a combination of Otake or Castor in view of Sachse and further in view of Mackaness; and

(2) Claims 21-42, 44 and 45 had been rejected as being unpatentable over a combination of Otake or Castor in view of Sachse and further in view of Klaveness.

The Examiner cited Otake and Castor in a previous Office Action dated July 29, 2008 to teach the formation of liposomes using supercritical carbon dioxide. The Examiner recognized that Otake and Castor do not teach increased encapsulation with the PEGylated form of the phospholipid. Applicants responded to this point made by the Examiner on November 19, 2008, by performing tests that showed that the liposomes made in accordance with the present Invention using either a phospholipid modified with a polyalkylene oxide or a compound containing a polyoxyalkylene group results in increased inclusion of the iodine compound compared to liposomes that are

made in accordance with Otake. These tests were reported by way of a Declaration by Mr. Nakajima, submitted on November 17, 2008.

In the present Office Action, the Examiner stated that the test data provided in the Declaration of Mr. Nakajima submitted on November 17, 2008 was not enough data to show unexpected results and pointed out that Otake teaches trapping efficiencies as high as 45% while the Declaration provides data for the Invention with a lower trapping efficiency, and did not provide for the amount of added water. To respond to these points, additional tests have been performed and are presented herein by way of a Declaration.

The trapping efficiency of the liposome depends on the ease of hydrating the substance to be encapsulated. With respect to the amount of added water, the ease of hydration of the substance to be encapsulated directly affects the amount of water added. For example, the iodine compound of the present invention, i.e. iohexol 300 mgI/mL, has an amount of water that is lower than 35% of the liposome. Thus, it is very difficult to hydrate and hard to encapsulate with a phospholipid. In contrast, the substance encapsulated in Example 4 of Otake is glucose which is very easy to hydrate and encapsulate with a phospholipid. Thus, even by choosing the same phospholipids, the value of the trapping efficiency of the liposome varies by

the substance to be encapsulated. The trapping efficiency of iohexol with DOPC is lower than that of a glucose with DOPC.

Additionally, in order to further respond to the Examiner's position, Applicants have submitted a Declaration demonstrating that the trapping efficiencies of the liposome is dependent on the substance encapsulated. The Declaration of Mr. Nakajima is attached hereto.

In order to show that the trapping efficiency of a liposome depends on the substance to be encapsulated by a phospholipid, Applicants have made four new liposomes, Samples 6-1 through 6-4. Each of the samples was prepared with DOPC as the phospholipid and the concentration of the phospholipid to the amount of added water was 20 mM. Sample 6-1, in which the substance encapsulated was glucose, was prepared as described in Example 4 of Otake. Sample 6-2 was prepared as Sample 6-1, except the substance to be encapsulated was iohexol in an amount of 647 mg/ml, having an iodine content of 300 mgI/mL. Therefore, the only difference between Sample 6-1 and Sample 6-2 was the substance to be encapsulated. Sample 6-3 was prepared in the same manner as Sample 6-1, except no ethanol was used. Sample 6-4 was prepared in the same manner as Sample 6-2 except no ethanol was used. Therefore, the only difference between Samples 6-3 and 6-4 was the substance to be encapsulated. The

trapping efficiency is reported in Table 6 of the attached Declaration.

As shown in Table 6, the trapping efficiency of Sample 6-2, containing iohexol, was much lower than that of the Sample 6-1 containing the glucose solution. In fact, the trapping efficiency of Sample 6-2 was less than half as efficient as Sample 6-1. The trapping efficiency of Sample 6-1 was more than two times the trapping efficiency of Sample 6-2. Samples 6-4, containing iohexol, has a lower trapping efficiency than Sample 6-3. The trapping efficiency of Sample 6-4 was almost half the trapping efficiency of Sample 6-3. The trapping efficiency of Sample 6-3 was more than one and a half times the trapping efficiency of Sample 6-4. Thus, the test results reported in Table 6 demonstrate that the trapping efficiency of a liposome depends on the substance to be encapsulated by a phospholipid.

In addition, Applicants note that the trapping efficiencies for Samples 6-1 and 6-2 containing ethanol were higher than those without ethanol. Otake teaches the use of ethanol in the process of preparing liposomes, whereas the present invention does not provide for the use of ethanol. Thus, one of skill in the art would not be motivated to eliminate the use of ethanol from the method of Otake.

Moreover, in order to show that PEGylated phospholipids provide improved encapsulation of iodine compounds, Applicants

have prepared a new set of liposomes using three different phospholipids. Samples 7-1 through 7-9 were prepared and tested to compare the amount of iodine included in the Otake liposomes to the amount of iodine included in liposomes made in accordance with the claimed invention. The liposomes made in accordance with the claimed invention contained either a phospholipid modified with a polyalkylene oxide or a compound containing a polyoxyalkylene group and a sterol. Applicants note that the concentration of the phospholipids with respect to the amount of added water was 20mM. The samples were prepared as follows:

a. Sample 7-1 was prepared with DOPC as the phospholipid in the same manner as described in Example 4 of Otake except that no ethanol was used and that the substance to be encapsulated was iohexol in an amount of 647 mg/ml, having an iodine content of 300 mgI/mL.

b. Sample 7-2 was prepared in the same manner as Sample 7-1, except that it also included DSPE-020CN, which is a phospholipid modified with a polyalkylene oxide, available from NOF Corporation.

c. Sample 7-3 was prepared in the same manner as Sample 7-1, except that it also included pluronic F-88, a compound containing a polyoxyalkylene group, available from ADEKA Co.

d. Sample 7-4 was prepared in the same manner as Sample 7-1, except that DPPC was the phospholipid used instead of DOPC.

e. Sample 7-5 was prepared in the same manner as Sample 7-2, except that DPPC was the phospholipid used instead of DOPC.

f. Sample 7-6 was prepared in the same manner as Sample 7-3, except that DPPC was the phospholipid used instead of DOPC.

g. Sample 7-7 was prepared in the same manner as Sample 7-1, except that DSPC was the phospholipid used instead of DOPC.

h. Sample 7-8 was prepared in the same manner as Sample 7-2, except that DSPC was the phospholipid used instead of DOPC.

i. Sample 7-9 was prepared in the same manner as Sample 7-3, except that DSPC was the phospholipid used instead of DOPC.

The proportion (weight percentage of iodine compound in the vesicle based on total iodine compound) of each of the samples is reported in Table 7 attached to the Declaration.

As noted in Table 7, the amount of iodine in the vesicle in Samples 7-2 and 7-3 was greater than the amount of iodine in the vesicle of Sample 7-1. Specifically, the amount of iodine encapsulated in Sample 7-2 was more than double and almost triple the amount encapsulated in Sample 7-1. The amount of iodine encapsulated in Sample 7-3 was more than one and a half times the amount encapsulated in Sample 7-1. Also noted in Table 7, the amount of iodine in the vesicle in Samples 7-5 and 7-6 was greater than the amount of iodine in the vesicle of Sample 7-4. In particular, the amount of iodine encapsulated in Sample 7-5 was about two times the amount encapsulated in Sample

7-4. The amount of iodine encapsulated in Sample 7-6 was more than one and a half times the amount encapsulated in Sample 7-4. Additionally, Table 7 also shows that the amount of iodine in the vesicle in Samples 7-8 and 7-9 was greater than the amount of iodine in the vesicle of Sample 7-7. The amount of iodine encapsulated in Sample 7-8 was more than one and a half times the amount encapsulated in Sample 7-7. The amount of iodine encapsulated in Sample 7-9 was almost one and a half times the amount encapsulated in Sample 7-7. Thus, the samples made in accordance with the claimed invention containing either a phospholipid modified with a polyalkylene oxide or a compound containing a polyoxyalkylene group and a sterol resulted in a surprising and unexpected improvement in an amount of iodine compound encapsulated in the liposome compared to the teaching of Otake.

Thus, the claimed invention yields surprisingly superior inclusion ratio over Otake. Respectfully, the claims, as presented herein, are patentable over the cited references taken alone or in combination.

E. Double Patenting Rejection

Claims 21, 22 and 26 had been provisionally rejected on non statutory obviousness-type double patenting based on Claims 1, 4, 6, 8-10 and 19 of copending Application 11/180,849; and

Claims 21, 22, 25 and 27 had been provisionally rejected on the non statutory obviousness-type double patenting based on Claims 1, 5-8, 10-12 and 14-17 of copending Application 11/187,397.

Terminal Disclaimers have been submitted for both Application 11/180,849 and Application 11/187,397.

F. Conclusion

In view of the foregoing and the enclosed, it is respectfully submitted that the Application is in condition for allowance and such action is respectfully requested. Should any extensions of time or fees be necessary in order to maintain this Application in pending condition, appropriate requests are hereby made and authorization is given to debit account # 02-2275.

Respectfully submitted,
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Attached: Executed Declaration of Mr. Akihisa NAKAJIMA
Terminal Disclaimer to Application 11/180,849
Terminal Disclaimer to Application 11/187,397